Listing of Claims:

1. (Previously Presented) A composition comprising an isolated polypeptide fragment of a mature mitochondrial MDH polypeptide that comprises an amino acid sequence that comprises a portion of SEQ ID NO:4, wherein said portion comprises SEQ ID NO:6 and has an activity selected from: DNA nuclease activation activity, and cell killing activity.

2. (Original) The composition of claim 1, wherein said portion comprises SEQ ID NO:7.

3. (Previously Presented) A composition comprising a conjugate that comprises an amino acid sequence comprising SEQ ID NO:6, wherein said amino acid sequence is operably linked to a first molecule that specifically binds to a cell molecule, wherein said conjugate activity is selected from DNA nuclease activation activity and cell killing activity.

4. (Original) The composition of claim 3, wherein said amino acid sequence comprises SEQ ID NO:7.

5. (Original) The composition of claim 3, wherein said amino acid sequence further comprises a N-terminal signal peptide.

6. (Original) The composition of claim 3, wherein said amino acid sequence further comprises a cell internalization peptide.

7. (Original) The composition of claim 3, wherein said amino acid sequence further comprises a nuclear localization peptide.

8. (Original) The composition of claim 3, wherein said first molecule comprises an antibody.

9. (Original) The composition of claim 8, wherein said antibody specifically binds to cancer cells.

10. (Original) The composition of claim 9, wherein said cancer cells are chosen from non-small cell lung carcinoma cells, breast cancer cells, gastrointestinal cancer cells, renal carcinoma cells, and liver cancer cells.

11. (Original) The composition of claim 10, wherein said cancer cells comprise liver cancer cells.

12. (Original) The composition of claim 11, wherein said liver cancer cells comprise hepatocellular cancer cells.

13. (Original) The composition of claim 11, wherein said antibody that binds to liver cancer cells comprises an antibody chosen from Hepama-1, anti-PLC1, anti-PLC2, K-PLC1, K-PLC2, K-PLC3, 49-D6,7-E10, 34-A4,26-A10, 34-B9,79-C8,16-E10, 5D3, 5C3, 2C6, a-AFP, H hHP-1, mAb 95, YPC2/38.8, P215457, PM4E9917, HAb25, HAb27, KY-1, KY-2, KY-3, 9403 Mab, KM-2, S1, 9B2, IB1, A9-84, SF-25, AF-10, XF-8, AF-20, a-hIRS-1, FB-50, SF 31, SF 90, 2A3D2, and 2D11E2.

14. (Original) The composition of claim 11, wherein said antibody that binds to liver cancer cells comprises Hepama-1 antibody.

15. (Original) The composition of claim 14, wherein said antibody comprising Hepama-1 antibody is humanized.

16. (Original) The composition of claim 9, wherein said cancer cells are chosen from B cell lymphoma cells, myeloid leukemia cells, renal carcinoma cells, colon cancer cells, pancreatic cancer cells, colorectal cancer cells, ovarian cancer cells, and prostate cancer cells.

17. (Original) The composition of claim 3, wherein said first molecule comprises a ligand of a cell receptor.

18. (Original) The composition of claim 17, wherein said ligand comprises a growth factor.

19. (Original) The composition of claim 18, wherein said growth factor is chosen from epidermal growth factor, insulin-like growth factor, fibroblast growth factor, and vascular endothelial growth factor.

20-47 (Cancelled).

REMARKS/ARGUMENTS

The Status of the Claims.

Claims 1-19 are pending with entry of this amendment.

The Information Disclosure Statement.

Applicants note with appreciation the Examiner's thorough consideration of the references cited in the Information Disclosure Statement (Form 1449) submitted on September 20, 2006.

35 U.S.C. §102.

Claims 1-5, 8, and 17 were rejected under 35 U.S.C. §102(b) as allegedly anticipated by Tang.

In order for a reference to anticipate an invention, the reference must teach each and every element of the claimed invention. To anticipate an invention, the law requires that "all limitations of the claim are found in the reference, or 'fully met' by it." Kalman v. Kimberly-Clark Corp., 218 USPQ 781, 789 (Fed. Cir. 1983).

The claimed invention is a composition "comprising an isolated polypeptide fragment of a mature mitochondrial MDH polypeptide". The polypeptide fragment "comprises an amino acid sequence that comprises a portion of SEQ ID NO: 4". The portion of SEQ ID NO: 4 comprises SEQ ID NO:6 and the composition has an "activity selected from: DNA nuclease activation activity, and cell killing activity". To anticipate this invention, Tang must teach a fragment of a mature MDH polypeptide, wherein the fragment comprises the SEQ ID NO: 6 portion of SEQ ID NO: 4 and exhibits cell killing or nuclease activity.

Tang teaches, if anything, a full-length mature MDH polypeptide. Tang does not teach a fragment of an MDH polypeptide and therefore all limitations of the claim are not found in the reference and it cannot anticipate the claimed invention.

In alleging that Tang anticipates the claims, the Examiner seems to focus on the use of the term "comprising" and the fact that Tang SEQ ID NO: 233 is 99.8% identical to Applicants' SEQ ID NO: 4. It appears that the Examiner believes that the fact that the Tang sequence is not 100% identical makes it a fragment and/or that Tang teaches a fragment and the remainder of the mature polypeptide is an optional unrecited element allowed by the use of the term "comprising".

The Examiner is correct in asserting that the claim is written in an open style and therefore does not exclude compositions containing the claimed sequences in combination with

unrecited extra elements. However, a composition that includes additional unrecited elements must still meet each and every limitation of the claim. One element of the claim is a fragment of a mature MDH polypeptide and no fragment is taught in Tang.

If anything, Tang teaches a conservatively modified variant of SEQ ID NO: 4, e.g. a mature MDH polypeptide that does not anticipate the claimed invention. Although the Tang sequence is not 100% identical to the MDH to which claim 1 refers, e.g., SEQ ID NO: 4, it is equivalent as described in the specification. MDH is described in the specification as an enzyme that is synthesized as a larger precursor molecule and then transported into the mitochondria where a signal sequence is cleaved to provide a mature MDH protein. See, e.g., page 33, line 30, to page 34, line 1, and page 36, lines 2-3. The specification further describes "MDH" molecules as including MDH variants of about the same molecular weight but with conservative substitutions. See, e.g., page 28, lines 18-23. Specific conservative substitution groups are listed on page 29, lines 1-5, and include the substitution of alanine for valine. The mature MDH molecule described in the specification differs from the Tang sequence by one conservative substitution: alanine (SEQ ID NO: 4) replaced by valine (Tang) at position 9. The sequence provided by the Examiner as an anticipating composition is a mature MDH sequence as defined in the present specification. Therefore, to anticipate the claimed invention, Tang must teach a fragment of SEQ ID NO: 233.

Tang does not, in any way, teach or identify an MDH fragment as defined in the instant specification and presently claimed. For example, the specification defines a fragment as being "from 4-50 or the entire amino acid sequence minus one amino acid residue," e.g., on page 27, lines 4-5. This definition is supported by various dictionary definitions. For example, the American Heritage online dictionary defines a fragment as "a small part broken from a larger entity" or "an incomplete or isolated portion". Meriam Webster defines a fragment as "a part broken off, detached or incomplete." A portion is defined as "a part of any whole" or "a part separated from a whole" in American Heritage and as "a part set off from the whole" in Meriam Webster. It is clear that the sequence taught by Tang is, if anything a mature, i.e., complete, variant of MDH, as it has a single conservative substitution of one aliphatic amino acid for another aliphatic amino acid (alanine for valine). The entire sequence of Tang, e.g., a mature MDH variant, does not teach a fragment, e.g., a small part isolated from the whole or an entire sequence minus at least one residue. Although one amino acid residue is different, SEQ ID NO: 233 of Tang is the same length as a mature MDH polypeptide and is not a fragment as claimed. Therefore, Tang cannot anticipate the claimed invention.

Although the Examiner compares sections of Tang's SEQ ID NO: 233 to SEQ ID NOs: 6 and 7 of the present invention and correctly notes that SEQ ID NOs: 6 and 7 are contained within SEQ ID NO: 233, nothing in Tang identifies those sequences as having any importance, i.e., they are not isolated or identified. Tang does not indicate or teach to one of skill in the art which sections of SEQ ID NO: 233 should be isolated and used in a composition as claimed. In Tang, the amino acid sequences to which the Examiner refers are merely present in the mature polypeptide; they have not been identified as fragments contributing to or having a particular activity when isolated from the mature polypeptide. Therefore, Tang does not teach a fragment of a mature MDH polypeptide as presently claimed.

Even if the Examiner persists in calling the sequence of Tang a fragment, it still cannot anticipate the claimed invention because it has not been shown to have the claimed cell killing and/or nuclease activity. In fact, SEQ ID NO: 4 and SEQ ID NO: 233 are 99.8% identical, which in this case is a difference of one conservative substitution. Conservative substitution is, as defined in the Encyclopedia of Molecular Biology, "The replacement of one amino acid in a polypeptide with another having similar properties. This kind of alteration is unlikely to change the structure or function of the resulting protein." For a prior art teaching to anticipate by inherency, the relevant limitations of the claim must be "**necessarily present.**" *Continental Can Co. USA v. Monsanto Co.*, 20 USPQ 2d 1746, 1749 (Fed. Cir. 1991). The mere fact that a certain thing may result from a given set of circumstances is not sufficient. SEQ ID NO: 233 in Tang does not necessarily have the activity claimed by applicants, e.g., cell killing or nuclease activity. In fact, it is unlikely that it would have the claimed activity as it is a conservatively modified variant of a protein that does not have the claimed activity. The claimed invention is based on the surprising discovery that specific fragments of a mature MDH polypeptide have cell killing or nuclease activity whereas mature MDH polypeptides do not. See, e.g., page 35, lines 15-22. Therefore, another equivalent mature MDH polypeptide is not **necessarily** going to have the activity that Applicants have already demonstrated is not present in mature MDH, but only in specific fragments. Tang does not teach the activity as claimed or any specific fragments that have the activity and cannot anticipate the claimed invention.

In conclusion, Applicants question, "Where in the prior art is a fragment identified, e.g., isolated from the whole MDH polypeptide?" Other than in the instant specification and claims, no isolated fragment of a mature MDH polypeptide is identified and there is no teaching to indicate that a mature MDH polypeptide has the claimed activity. Therefore, the claims are novel and Applicants respectfully request that the rejections be withdrawn.